METHYL tert-BUTYL ETHER

CAS number: 1634-04-4

Synonyms: tert-Butyl methyl ether; 2-Methoxy-2-methylpropane; 2-Methyl-2-methoxypropane; Methyl-1,1-dimethylethyl ether; MTBE

Molecular formula: $C_5H_{12}O$

Structural formula: $(CH_3)_3COCH_3$

TLV–TWA, 50 ppm (180 mg/m^3)

A3 — Confirmed Animal Carcinogen with Unknown Relevance to Humans

Summary

A TLV–TWA of 50 ppm is recommended for occupational exposure to methyl tert-butyl ether (MTBE). This value is based on no symptoms noted in a chamber study of 10 subjects exposed up to a 50-ppm concentration, a no-observed-adverse-effect level (NOAEL) for repeated inhalation exposure of rats at 800 ppm, the NOAEL of 400 ppm in rats from a two-generation study, and with renal toxicity noted in rats (both the dams and offspring) following inhalation at 300 and 3400 ppm, and taking into account the preferred value approach.

At present, most occupational exposure to MTBE is through exposure to gasoline; in this case, the TLV for gasoline should be consulted. Also of note is the use of MTBE in transhepatic instillation for treatment of gallstones; at this point, there exist no relevant data for exposed healthcare workers.

MTBE is classified as an A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans, given the predominantly negative mutagenicity data and the significantly increased cancers in both sexes of mice and rats, particularly α_2-microglobulin male rat kidney tumors and female mouse hepatic tumors. At present, there is insufficient evidence to evaluate the carcinogenicity of MTBE to humans. Because several groups of exposed workers are likely to have skin exposure, multiple routes of exposure must be considered in future research. Sufficient data were not available to assign Skin or sensitization (SEN) notations or recommend a TLV–STEL.

Although crucial to the long-term use of MTBE as an important fuel additive, the issues of environmental and drinking water contamination with MTBE and the possible carcinogenic and other health risks to humans are beyond the scope of this *Documentation* since this does not represent a typical occupational exposure scenario.

Chemical and Physical Properties

Methyl tert-butyl ether (MTBE) is a colorless liquid with an unpleasant hydrocarbon odor. It is flammable when exposed to heat or flame, and when heated, it emits acrid smoke and irritating fumes. Chemical and physical properties include:[1–10]

- Molecular weight: 88.17
- Specific gravity: 0.75 at 20/4°C
- Freezing point: –109°C
- Boiling point: 55.2°C
- Vapor pressure: 245 torr at 25°C
- Flash point: –28°C
- Explosion limits: upper, 15.1%; lower, 2.5% by volume in air
- Solubility: insoluble in acid solutions; moderately soluble in water (4.8 g/100 g); very soluble in alcohol and ether
- Odor threshold: 0.32 to 0.47 mg/m^3
- Odor threshold of 97% pure MTBE in gasoline: 0.50 ppm (3% MTBE), 0.28 ppm (11% MTBE), 0.26 ppm (15% MTBE)
- Conversion factors at 25°C and 760 torr: 1 ppm = 3.60 mg/m^3; 1 mg/m^3 = 0.28 ppm

In the presence of atmospheric oxygen, ethers generally form unstable peroxides, but no peroxides were detected in unstabilized MTBE after storage for 52 months.[11] MTBE has a significantly decreased formation of peroxides compared with other ethers.[3,12]

Major Sources of Exposure

Uses

MTBE is used almost exclusively as a blending component or octane-enhancing agent in gasoline, with typical concentrations ranging from 5% to 10% by volume, although they can be up to 17%.[5,9,10,13] MTBE also frees up toluene that might otherwise have been added to gasoline pools in order to meet unleaded octane requirements.[6]

Its use in gasoline has been encouraged by the U.S. Environmental Protection Agency (EPA) as part of their oxygenation program to decrease carbon

monoxide production from internal-combustion-engine emissions in northern areas during the cold winter months, especially in older cars.[14–16] MTBE was approved as a blending component in 1979 by EPA, with a significant increase in both national manufacture and importation since then. In 1992, those areas of the United States where the carbon monoxide standard exceeded national standards, MTBE was raised to 15% by volume to reduce atmospheric pollution.[17] There is considerable concern in EPA with regard to possible ground water contamination with MTBE via leaking underground gasoline storage tanks, especially since the presence of MTBE appears to increase the solubility of gasoline in water; the unpleasant odor of MTBE even in ground water contamination situations may have useful warning properties.[5,13,18–21]

Since 1981, MTBE has been used in medical procedures to dissolve gallstones in humans. This use is expected to expose health care workers and patients, although to relatively small amounts (i.e., enough to fill the gallbladder continuously through a percutaneous transhepatic catheter 5 hours/day for 1 to 3 days). MTBE is an excellent cholesterol-solubilizing agent, and as opposed to diethyl ether, it is a liquid at human body temperature and less volatile.[12,13,21–24]

MTBE has been used as a chromatographic eluent for liquid and thin-layer chromatographic procedures and as a solvent in the determination of resin and fatty acids in pulp mill effluents.[3,19] A small amount of MTBE is used in the manufacture of isobutene.[5] MTBE is not known to occur naturally in the environment. MTBE is commercially produced in a closed system process by the reaction of isobutylene and methanol in the presence of an acid ion-exchange resin catalyst[12] or via catalytic reaction of methyl alcohol and isobutene (38°–93°C at 100–200 psi).[2,6,9,10]

In 1978, the world capacity to produce MTBE was only 300 million pounds. With the use of MTBE as a gasoline additive, it has become the fastest growing chemical product in U.S. industry.[6,12,18,26] In 1994, the worldwide production was 20.6 million tons and in 1996, the U.S. production capacity was 10.6 million tons; approximately 25% of the gasoline in the U.S. is blended with MTBE added in concentrations up to 17% by volume.[9,10,27]

Exposures

Workers exposed to MTBE include radiologists, life scientists, clinical laboratory technicians, production testers, those involved in transport of MTBE, and gasoline station attendants and consumers who pump gas. At least 2570 workers are exposed to MTBE directly, with 35,000 other workers exposed during bulk shipment of gasoline and many more exposed at retail gasoline outlets of which the vast majority are self-service.[11,13]

Occupational exposures (in closed systems) in refineries are reportedly generally less than 1 ppm (3 mg/m^3) for an 8-hour TWA; the highest level of MTBE vapor reported was a TWA of 33 ppm (100 mg/m^3) with a short-term exposure of 45 ppm (135 mg/m^3).[13] Lillquist and Zeigle [28] evaluated MTBE exposures in petroleum refinery and transport loading rack facility employees; the TWA samples ranged from < 0.042 to 1.75 ppm, the personal STEL sampling ranged from < 0.0896 to 35.012 ppm (geometric mean, 2.44 ppm) and personal TWA sampling from < 0.042 to 1.75 ppm (geometric mean, 0.58 ppm). Short-term exposure during bulk loading/unloading of MTBE has been estimated to be as high as 550 ppm (1650 mg/m^3).[13,29] Vainiotalo et al. [30] evaluated exposure to MTBE and tert-amyl methyl ether (TAME) from gasoline during tank loading in Finland. Geometric mean of MTBE was 4.3 to 6.4 mg/m^3 (1.2–1.7 ppm) (somewhat higher in the summer) with an overall range of 0.75 to 33.7 mg/m^3 (0.21–9.36 ppm).

Exposure of service station attendants has been reported as 8.6 ppm (31 mg/m^3) for an 8-hour TWA,[13] and even less exposure reported with vapor recovery equipment installed.[31] In a U.S. National Institute for Occupational Safety and Health (NIOSH) study, Cook and Kovein[3] reported a geometric mean TWA of 0.38 ppm (range, 0.08–1.3 ppm) for gas station attendants; however real-time monitoring for total hydrocarbons raised the possibility of elevated peak concentrations 130 times greater than TWA concentrations. Monitoring data of workers and commuters were performed by the American Petroleum Institute (API).[15] The majority (96%) of manufacturing and transport workers were found to be exposed to less than 100 ppm as a TWA with 98% of short-term excursions to be less than 300 ppm. API found lower exposures for service station workers (maximum level below 2.6 ppm with the mean below 1 ppm over 4 hours in the breathing zone and at the pump island). Even lower exposures were found for commuters, ranging from 1.2 to 160 ppb over 1 hour in the cabin interior.[15,33–35] Vainiotalo et al.[36] studied customer exposure to gasoline and its constituents during the summer in Finland. The overall geometric mean for an adjusted 1-minute refueling time for MTBE was 3.3 mg/m^3 (0.92 ppm) with a MTBE content of 12.2% of gasoline.

White et al.[37] evaluated venous blood samples and some air samples from 14 commuters and 30 other persons working in the vicinity of automobiles or traffic in Connecticut. Samples were analyzed for MTBE, tert-butanol, benzene, m/p xylene, o-xylene, and toluene. The highest blood levels of MTBE were found among gasoline service station attendants (median, 15 μg/L; range, 7.6–28.9 μg/L), while other levels varied among car repair personnel (median 1.73 μg/L; range, 0.17–36.7 μg/L) to the lowest among commuters (median 0.11 μg/L; < 0.05–2.60 μg/L). TWA concentrations among mechanics

repairing motor vehicles ranged from undetectable to 12.04 ppm. Of note, personal breathing zone concentrations of MTBE correlated strongly with those of benzene ($r = 0.95$; $p < 0.0001$).

Moolenar et al.[38] of the U.S. Centers for Disease Control and Prevention (CDC) and the Alaska Health Dept evaluated 18 workers (service station attendants, garage workers, drivers, and mechanics) during the active use of MTBE as a gasoline additive in December 1992 and 28 workers after the use of MTBE was suspended in February 1993. All workers were heavily exposed to motor vehicle exhaust or gasoline fumes. In December, the median postshift blood concentration of MTBE was 1.8 μg/L (0.2–37.0 μg/L), and in February, the median MTBE blood level was 0.24 μg/L (0.05–1.44 μg/L), which was a statistically significant difference ($p = 0.0001$). Median MTBE blood levels also evaluated among 7 commuters before and after their commute during December (before, 0.18 μg/L; after 0.83 μg/L) were significantly higher than February (before, 0.09 μg/L; after 0.10 μg/L; $p = 0.04$).

Animal Studies

The toxicology of MTBE has been summarized,[9,10,17,27,39–42] and only those data utilized in the derivation of the TLV are cited below. In general, MTBE is characterized as being mildly to moderately toxic in rodents following inhalation, oral, or cutaneous exposure both acutely and chronically. The major findings have been mild irritation to eyes and mucous membranes, transient depressant effects on the central nervous system (CNS), and increased hepatocellular carcinoma in female mice and increased renal cancers in male rats (the latter associated with α_2-microglobulin nephropathy).[43]

Acute

Marsh and Leake[8] conducted acute inhalation experiments with mice (20 per group) on the anesthetic and lethal activity of MTBE. The LC_{50} was 39,120 ppm; the concentration required to anesthetize 9 to 11 of the 20 mice (AC_{50}) was 24,450 ppm. Reynolds et al.[44] reported an oral LD_{50} of 4 ml/kg and a 4-hour inhalation LC_{50} of 23,576 ppm for rats. Conaway and associates[45] reported an inhalation LC_{50} of approximately 35,000 ppm for the Sprague–Dawley rat. A single-dose dermal LD_{50} for rabbits was reported as > 10 mg/kg.[44]

ORAL

In acute gavage studies in rats, death was preceded by marked CNS depression, ataxia, tremors, labored breathing, and loss of righting reflexes; animals that survived were normal within 24 hours from exposure.[26] In acute inhalation studies in rats, death was preceded by eye irritation, irregular respiration, incoordination, and prostration.[26] The addition of MTBE to gasoline up to 10% to 15% (v/v) did not increase acute toxicity of gasoline; however, it did lengthen barbiturate-induced sleep time, reduce spontaneous motor activity, and cause slight disturbances in motor coordination in rats.[45]

In a 14-day oral toxicity study,[25] 50 male and 50 female Sprague–Dawley CD rats were fed MTBE in four treatment groups at 357, 714, 1071, or 1428 mg/kg/day with one control group receiving the corn oil vehicle. A concurrent 90-day study fed rats in four treatment groups with exposure up to 1200 mg/kg/day. At 1200 mg/kg and 1428 mg/kg, MTBE induced anesthesia that lasted about 2 hours, followed by an uncomplicated recovery. There were no deaths attributable to MTBE exposure; diarrhea was common to all treatment groups. Of note, oral dosing was difficult due to reported irritation of the pharyngeal region of the rats receiving higher doses. Food consumption and body weight gain were significantly decreased in the higher dose groups. Lung weights were reduced and liver weights increased in the highest dose females; kidney weights were increased in the highest dose males with a similar, but not significant, trend among the females. There were also trends toward increased serum cholesterol levels in both sexes and increased blood urea nitrogen (BUN) and creatinine levels in females with increasing dose. The incidence of renal tubular disease (nephropathy), characterized by increased hyaline droplets within the cytoplasm of the proximal tubular epithelial cells, was recorded in seven of eight high-dose males and in only two of five controls.

INSTILLATION

Most acute animal toxicology data available on MTBE have been generated by studies concerning the transhepatic instillation of MTBE for the purpose of dissolving gallstones. In dogs undergoing experimental intrahepatic instillation, intermittent vomiting and transient, mild salivation were noted in four of six animals.[22] In another study with dogs and intrahepatic instillation, mild duodenitis and a two- to fourfold increase of alkaline phosphatase with no other liver function abnormalities were noted.[23]

In rabbits with surgically implanted human gallstones and infusion of dimethylsulfoxide (DMSO) and MTBE, there were no acute effects; at 15 days from perfusion, the residual histopathotoxicity was minimal, and there was no difference in the blood or liver parameters when compared with those prior to treatment.[46] In another study with rabbits undergoing MTBE instillation,[47] the animals experienced transient vomiting, dyspnea, characteristic breath odor, and somnolence. There were post-treatment significant increases in serum transaminases and alkaline phosphatase compared with saline-treated controls. Necropsy revealed histologic evidence of chemical cholangitis (inflammation of the bile duct) and mild duodenitis in the MTBE-treated animals.

Respiratory

Respiratory irritancy was examined at five MTBE concentrations (300 to 30,000 mg/m^3) in mice for 1 hour.[48] The severity of sensory irritation ranged from slight at 300 mg/m^3 to severe at 30,000 mg/m^3; pulmonary irritation was suggested only at 30,000 mg/m^3 (8333 ppm). The authors[48] used interpolation and the 1984 Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals developed by the American Society for Testing and Materials to estimate whether an 8-hour exposure at 500 mg/m^3 (139 ppm) would be considered for healthy humans to be free from significant sensory irritation.

An acute (6-hour) vapor inhalation study was performed on 176 Fischer 344 rats (22/sex/group) at 0, 800, 4000, or 8000 ppm of MTBE. A functional observation battery was employed to evaluate neurobehavioral function at 1, 6, and 24 hours postexposure on 8 animals/sex/group; the remaining 14 animals/sex/group were evaluated for changes in motor activity. There was no mortality or overt toxicity reported in any dosage group. At 1-hour post-exposure, some changes were noted in the functional observation battery at 4000 and 8000 ppm, including ataxia and duck walk-like gait in both sexes as well as decreased muscle tone, decreased hindlimb grip strength decreased treadmill performance, and decreased body temperature. Increased lacrimation was attributed to the irritative nature of high vapor concentrations of MTBE. Motor activity was increased at 800 and 4000 ppm and decreased at 8000 ppm compared with controls during the initial 10 minute session. The authors[49–51] state that these results are indicative of transient CNS sedation associated with inhalation exposure to elevated levels of MTBE.

A 9-day inhalation study[11] with Sprague–Dawley CD rats exposed in groups of 20 for 6 hours/day, 5 days/week at 0, 100, 300, 1000, or 3000 ppm MTBE vapor produced no treatment-related mortality. Mean phosphorus levels were significantly elevated in the fasted females at the two highest concentrations. There was a statistically significant increase in liver weights in fasting animals of both sexes exposed at 3000 ppm and in the unfasted male animals. Gross pathology did not indicate any compound-related effects. However, microscopic pathology revealed chronic inflammation in the nasal mucosa and trachea of rats from the 1000 and 3000 ppm-exposed groups.

In a 10-day inhalation study of Fischer 344 rats by Prescott-Mathews et al.[52] male and female rats were exposed to MTBE vapors at 0, 413, 1516, and 3013 ppm for 6 hours/day. There was a statistically significant increase in liver weights for the highest exposure female group only; histologic examination was not performed. Significant proximal tubule necrosis and protein droplet accumulation was noted in the male rat kidneys exposed at the two highest doses; α_2-microglobulin immunoreactivity was present and confined to the protein droplets of these male rat kidneys, without accumulation of any other protein. There was a strong positive correlation ($r = 0.994$) with exposure concentration between cell proliferation and α_2-microglobulin in the male, but not the female, rat kidney. The authors[52] concluded that MTBE causes a mild induction of α_2-microglobulin nephropathy in male rats, suggesting a role for α_2-microglobulin nephropathy in renal tumorigenesis.

Unpublished results from a 28-day inhalation study[53,54] of MTBE vapor in F334 rats and CD-1 mice (cell proliferation assay data collected from rat kidney and mouse liver at 5 days, 4 weeks, and 6 weeks) indicated an increase in cell proliferation of kidney proximal tubule cells in male rats exposed at 3000 or 8000 ppm, but after 6 weeks, no increase was observed; female rats were not affected. Specific immunohistologic staining of male rat kidney sections tentatively identified α_2-microglobulin as the intercellular protein that accumulated coincident with cell proliferation.

Eye

MTBE is mildly irritating to the rabbit eye.[25] In a study reported by the U.S. EPA,[11] irritation was seen in both the washed and unwashed eyes of the test animals. One sample induced corneal opacities and conjunctival edema (chemosis) in three unwashed eyes. A second sample induced conjunctival redness through 72 hours in two rabbits. All rabbits tested with another sample were normal at 72 hours.

Skin

In dermal toxicity studies with rabbits,[11] samples of MTBE were applied to intact and abraded skin. Although one sample of MTBE did produce slight to severe erythema and blanching in two of six rabbits, the test material was not considered to be a primary irritant. Histologic evaluation showed variable findings from slight acanthosis to slight focal epidermal necrosis at the abraded site. The more severe finding was thought to result from an ectoparasite or trauma. MTBE caused only slight skin irritation when held in contact with guinea pig skin under an impervious cover for 24 hours.[11]

In skin sensitization studies,[11] MTBE failed to produce a significant response to the challenge injection as compared with the initial sensitizing injection. MTBE induced local skin irritation with 0.5 ml of a 0.1% solution.

Subchronic

Oral

A 90-day consecutive oral toxicity study[26] used 50 male and 50 female Sprague–Dawley CD rats in four treatment groups exposed at five daily doses (100, 300, 900, or 1200 mg/kg/day) with one control group receiving the corn oil vehicle. At or above 1200 mg/kg, MTBE induced anesthesia that lasted

about 2 hours; an uncomplicated recovery ensued. There were no deaths attributable to MTBE exposure; diarrhea was common to all treatment groups. Increased cholesterol and decreased BUN levels were seen in the females, with decreased creatinine in the males. In the high-dose male group, there were increased hematocrit and hemoglobin compared with controls. Increased liver and kidney weights were found among the high-dose males, and increased kidney weights were found among the females. Microscopic findings in most organs were unremarkable. In male rats, chronic nephropathy was common in both the high-dose and control groups, although graded more severe in the treated rats. Five of ten high-dose males had small numbers of tubules plugged with granular cases, and all the males in this group had slightly increased numbers of cytoplasmic hyaline droplets in the proximal tubular epithelial cells. These renal changes were consistent with α_2-microglobulin nephropathy, although appropriate protein staining was not reported.

Respiratory

Fischer 344 rats (25/sex/group) were exposed 6 hours/day, 5 days/week for 13 weeks at 0, 800, 4000, or 8000 ppm MTBE vapor.[47,55–57] The highest dose was selected due to the explosive nature of MTBE (i.e., 50% of the lower explosion limit). There were no mortalities. In the highest exposure (8000 ppm) group for both sexes, body weight gains and food consumption were depressed during the first 3 weeks of the study which resulted in lower weight gains for this group throughout the study. Male rats in the 4000-ppm group also had depressed weight gain during the first week of the study. Male and female rats had increased liver and kidney weights in the MTBE-exposed groups. Adrenal weights were increased in all males of all MTBE-exposed groups and only in the females of the highest dose group. There were no exposure-related microscopic changes in these organs. There was a higher incidence of lymphoid hyperplasia in the lymph nodes of the male rats in the 8000-ppm group; these same males also had increases in the degree of hemosiderosis within the spleen and the size of hyalin droplets in the renal proximal tubules. Body weights were slightly decreased. In the MTBE-exposed groups, the corticosterone levels were increased at the highest dose. A trend was present for exposed rats of both sexes to have increasing serum aldosterone and corticosterone; there was also a trend of decreasing adrenocorticotropic hormone (ACTH) in the males. Both male and female rats had decreased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity in the serum. MTBE-exposed males had a decrease in red blood cell counts and an increase in the red cell indices, followed by an increased reticulocyte count; in the high-dose males, glucose was decreased and calcium and phosphorus increased. Serum albumin, globulin, and total protein were increased in the two highest dose male groups. The authors[55–57] concluded that these clinical pathologic changes could be attributed to stress.

In this same study,[50,51,55,58] subchronic neurotoxicity of MTBE was measured. The animals were evaluated with a functional observation battery before exposure and at weeks 1, 2, 4, 8, and 13; motor activity was evaluated before and at weeks 4, 8, and 13; neuropathologic examinations were performed on selected animals. Throughout the 13 weeks, ataxia and hypoactivity were observed daily in the highest dose group, while only hypoactivity was observed daily throughout the study in the 4000-ppm group. No persistent or cumulative effects on neurobehavioral function were found. There were minor changes in the functional observation battery at 4000 and 8000 ppm, including elevated body temperature in the high-dose males at week 1 and in the two highest dose female groups at week 13, and decreased hind limb grip strength in male rats of the 4000-ppm group only. There was a decrease in motor activity for the 8000-ppm males at week 8 only. The female rats exposed at 800 and 4000 ppm had an increase in motor activity at week 8 and only in the 4000-ppm group at week 13. Body weights and absolute brain weights were reduced in the 8000 ppm group although not when expressed relative to total body weight. No treatment-related microscopic changes of the neurologic system were noted. The authors,[50,51,55,58] concluded based on this and the previously described acute study, that MTBE does not appear to be a neurotoxicant. The no-observed-adverse-effect level (NOAEL) for repeated inhalation exposure to rats was 800 ppm.

Four groups of 3-month-old male Wistar rats (20 per group) were exposed 6 hours/day, 5 days/week for 2 to 15 weeks at 0, 50,100, or 300 ppm of MTBE vapor.[59,60] Exposure caused a transient dose-dependent increase in uridine diphosphate-glucuronosyltransferase activities in liver and kidney microsomes, almost no effects on hepatic cytochrome P-450 concentrations, and a minor induction of kidney microsomal cytochrome P-450 content. Exposure had almost no effect on brain succinate dehydrogenase, creatinine kinase, or acetylcholinesterase activities. Early inhibition of muscle creatinine kinase activity was noted, accompanied by increased activity at the end of exposure.

In a 90-day inhalation study[11] with male and female Sprague–Dawley rats exposed 6 hours/day, 5 days/week at target concentrations of 250, 500, or 1000 ppm, increasing sedation was noted with increasing MTBE concentration. Slight, insignificant reduction in body weight gain was seen at 1000 ppm. An increase in hemoglobin levels was noted at 1000 ppm in male rats at the termination of the study. Absolute and relative lung weights in females exposed at 1000 ppm were slightly reduced.

Chronic/Carcinogenicity

The carcinogenicity of MTBE in animals has been extensively reviewed.[9,10,27,41,42,61–64] In chronic rodent studies, MTBE exposure has been associated with increased hepatocellular carcinoma in female mice and increased renal cancers in male rats (the latter associated with preceding α_2-microglobulin nephropathy). An increase in interstitial cell testicular tumors in rats apparently was not significant because these tumors were commonly increased in aging rats of the particular strains studied.[17] A study[65,66] reporting increases in lympho-hematopoietic and male Leydig cell cancers in rats exposed through gavage with high doses of MTBE in olive oil has been questioned[17] due to spontaneous cancer incidence in the rat population and the exposure and analysis methodologies.

Belpoggi et al.[65,66] reported on the results of a chronic oral MTBE gavage study in 8-week-old male and female Sprague–Dawley rats (60/sex/group) given olive oil, 250 mg/kg of MTBE in olive oil, or 1000 mg/kg of MTBE daily 4 times/week for 104 weeks, then held until death or natural death (last died at 174 weeks of age). There were no differences in food consumption and mean body weight among the groups. The male mortality in the treated groups was equal to the control until week 80, when there was higher survival of the males at the higher dose. A dose–response decrease in survival was observed among the females from 16 weeks in the dosed groups compared with controls. No behavioral changes or noncarcinogenic systemic changes were noted. There was no increase in kidney tubule tumors. There was a reportedly statistically significant increase ($p < 0.05$) in testicular Leydig cell tumors at the higher dose in male rats, i.e., 11 tumors (18.3%) at 1000 ppm versus 2 tumors (3.3%) at 250 and 0 ppm were seen in the animals that survived to study termination. This did not take into account animal deaths from other causes in the calculation of tumor prevalence. Among female rats, there was a dose-related increase in lymphomas and leukemias (12[20%] versus 6[10%] versus 2[3.3%]), significantly higher ($p < 0.01$) at the highest dose level; the incidence among the male rats was slightly lower at the higher dose and within expectations of the historical controls. There was reportedly an increase in dysplastic proliferation of lymphoreticular tissue (defined by the authors as atypical lymphoid cells usually lymphoimmunoblasts) in the female rats at both doses, although higher among the lower dose animals (9 [15%] versus 15 [25%] versus 1 [1.7%]). At the lower dose, there was reportedly an increase in the incidence of uterine sarcomas in the female rats. Dose-related decreases were described in female rats for mammary fibromas and fibroadenomas, pituitary adenomas, and tumors of the adrenal glands. Of note, the data were reported as prevalences not as incidence rates making comparison between groups inappropriate; combining lymphomas and leukemias is highly questionable, leading to possible over estimation.[63,64] Finally, the development of the male Leydig cell tumors has been attributed to aging in these rat populations rather than MTBE exposure due to increased survival in the exposed populations.[17,63,64,67–69]

In chronic vapor inhalation studies[53,70–73] of Fisher 344 rats and CD-1 mice (50/sex/group) exposed at concentrations of 0, 400, 3000, or 8000 ppm of MTBE planned to last for 24 months (rats) and 18 months (mice), both species showed reversible CNS depression at 8000 ppm during and for up to 2 hours post exposure. Excessive mortality and decreased survival time were observed for male mice in the 8000-ppm group. Excessive mortality was observed in male rats exposed at the two highest levels, leading to early sacrifice at week 97 (3000-ppm group) and week 82 (8000-ppm group); the mortality and survival time for female rats was equivalent in all exposure groups. There was a 29% depression in body weight gain of the high-dose males by week 81, and a 23% depression in body weight gain of the high-dose female rats by week 103. It would appear that the maximum tolerated dose had been exceeded in these studies.

In the studies described above,[70–73] there was a statistically significant increase in chronic progressive nephropathy at 3000 and 8000 ppm which was the main cause of death among the male rats. In the 400-ppm group, there was also a slight increase in mortality and decrease in mean survival time for the males which was considered due to an increase in the severity of the nephropathy. The other major cause of death in this group was large granular lymphocyte leukemia; however, it was the main cause of death for the control group males as well, and no dose–response was observed for either males or females. There was a statistically significant increase (8/50) of renal tumors, tubular adenomas, and carcinomas at 3000 ppm; the incidence of renal tumors was also elevated (3/50) at 8000 ppm, although not statistically significant and probably due to the early mortality. For males, given the slight increase in chronic progressive nephropathy at 400 ppm, a no-observed-effect-level (NOEL) could be determined; for females, the NOEL was 400 ppm for toxic effects and 8000 ppm for oncogenic effects.[53,70–73]

In male rats, there was also a statistically significant increased incidence of testicular tumors (interstitial adenomas) compared to concurrent controls with a positive dose–response trend, e.g., 32/50 in controls, 35/50 in the 400-ppm group, 41/50 in the 3000-ppm group, and 47/50 in the 8000-ppm group.[14,53,54,71,73] These particular cancers, however, have been attributed to aging in these rat populations.[17,63,64,67–69]

In mice, there was increased mortality for males and a 15% decrease in body weight gain at the highest dose. The increased mortality may have

been due to the increased frequency of obstructive uropathy (urinary bladder dilation and distension). Female survival was not affected, but there was a 24% depression of body weight gain. No exposure-related hematologic changes were noted in any dose groups except for an increase in corticosterone levels in males and females in the highest level. Urinalysis results showed a decrease in urinary pH in both sexes from the highest concentration group and an increase in the gamma globulin fraction for male mice in the highest dose group. Increased liver weights and hepatocellular hypertrophy were reported for both sexes in the 8000-ppm group and for males in the 3000-ppm group. In male mice, there was an increased incidence of liver masses (13/50 versus 7/50 controls), a statistically insignificant increased incidence of hepatocellular adenomas and carcinomas (16/49 versus 12/49 controls), and a significantly increased incidence in the 8000 ppm group (8/49 versus 2/49 controls). In female mice, there was a statistically significant increase in hepatocellular adenomas at the 8000 ppm exposure only (10/50 versus 2/50 controls); no increase in hepatocellular carcinomas was seen for exposed females. There was a decreased incidence of cystic and polypoid endometrial hyperplasia in the females, which suggests an anti-estrogenic effect according to the authors.[53,71,72] [The 1993 EPA report[14] states that, because the mouse study was less than lifetime (i.e., 18 months, not 2 years), reduced duration of exposure reduced the sensitivity of the bioassay.] The NOEL was 400 ppm for toxic effects in mice, 3000 ppm for oncogenicity in female rats, and 8000 ppm for male rats.[53,71,72]

Moser et al.[74] had previously demonstrated that unleaded gasoline has hepatic tumor-promoting activity in N-nitrosodiethylamine initiated female B6C3F1 mice. These researchers hypothesized that MTBE would have hepatic tumor-promoting activity in a similar initiation-promotion model system. Twelve-day-old female mice received a single intraperitoneal injection of N-nitrosodiethylamine or saline. At 8 weeks of age, mice were exposed by inhalation at 0 ppm or 8000 ppm MTBE (the latter stated to be a hepatocarcinogenic dose) for 13 and 32 weeks. The MTBE-exposed group had significantly increased liver weight and hepatic microsomal P-450 activity, without hepatotoxicity or increase in nonfocal hepatocyte DNA synthesis. At 16 and 32 weeks, the MTBE did not significantly increase the mean size of hepatic foci and the volume fraction of liver occupied by foci as compared to the N-nitrosodiethylamine-initiated controls. The authors[74] state that this demonstrates that MTBE does not cause tumor promotion through the same pathway as unleaded gasoline. Additional studies by Moser et al.[75] with gavage administration of MTBE and unleaded gasoline to female B6C3F1 mice showed an increase in hepatic estrogen metabolism and uterine effects with both substances. The authors[75] suggest that these effects support a potential role for endocrine modulations in MTBE-induced hepatocarcinogenesis in mice. Of note, in a separate study, Moser et al.[76] showed that MTBE does not produce its antiestrogenic effects through interaction with the estrogen receptors.

Reproductive/Developmental

MTBE has not been found to induce major adverse effects on the fetal development of rats, mice, or rabbits; no major adverse effects on reproduction in one- and two- generation studies have been reported.[17]

One hundred mated CD Sprague–Dawley rats and CD-1 mice exposed by inhalation during the period of organogenesis at concentrations of 0, 250, 1000, or 2500 ppm MTBE resulted in no maternal mortality.[45] There were no changes in maternal body weight, water consumption, and liver weight or in the results of physical examination for either species. Food consumption was reduced in rats (days 9–12) and in mice (days 12–15). In rats, no changes in uterine implantation, fetal size parameters, or fetal sex ratio were noted. No external abnormalities, skeletal malformations, or ossification variations were reported for fetal rats. A slight increase in resorptions was observed in mice at the low and high concentrations which may not have been related to treatment. No significant effects on external or soft tissue, skeletal, or ossification parameters were noted in fetal mice. In fetal mice recovered from dams exposed at 2500 ppm, the incidence of fused sternebrae was increased, which may be attributed to fetotoxicity.

Male rats exposed to MTBE 6 hours/day, 5 days/week for 12 weeks at 300, 1300, or 3400 ppm were mated to female rats exposed for 3 weeks at the same concentrations.[77] Exposures continued through the mating period, during subsequent gestation, and from days 5 to 21 of lactation. A second litter was produced under similar conditions. No adverse effects were noted among any of the adult rats except for an increased incidence of dilated renal pelvices in the low- and high-dose females. Mating and fertility indices were not significantly different from controls. Pregnancy rates were slightly but not statistically lower among the second litter females compared with controls. Mean durations of gestation and pup numbers were comparable. The second litter displayed a slight but statistically significant difference in pup viability from controls; however, litter survival was comparable among all three groups. Pups of mid- and high-dose females had slightly lower but not statistically significant mean body weights at days 14 and 21. The most frequent post-mortem observation at day 21 of lactation was dilated renal pelvices, but there was no indication of a dose–response relationship.

Developmental toxicity studies were conducted in timed-pregnant New Zealand white rabbits (15 per group) and CD-1 mice (30/group).[78–81] Exposures at 0, 1000, 4000, or 8000 ppm of MTBE vapor occurred during organogenesis (gestational days 6–18 for the rabbit and 6–15 for the mouse). On gestational day 18 and 29, respectively, maternal mice and rabbits were sacrificed. For both species, pregnancy rate was high and equivalent across all groups; no pregnant animals died or aborted. Significant reductions in weight gain and food consumption were noted at 4000 and 8000 ppm for rabbits and at 8000 ppm for mice. Hypoactivity and ataxia were noted at 8000 ppm for rabbits and at 4000 and 8000 ppm for mice. Gestational parameters were unaffected in rabbits, and there were no exposure-related malformations in rabbits. Fetal body weights in mice were reduced at 4000 and 8000 ppm, and the number of viable implants/litter and sex ratio were reduced at the 8000-ppm level. An increase in cleft palate was observed at 8000 ppm, and an increase in skeletal variations was noted at 4000 and 8000 ppm in mice. The authors[78] stated that the NOEL was 1000 ppm for maternal toxicity and at least 8000 ppm for developmental toxicity in the New Zealand white rabbits. The NOEL for both maternal toxicity and developmental toxicity was 1000 ppm for CD-1 mice.[78–82]

In a two-generation reproduction study,[83–85] juvenile Sprague–Dawley rats (25 rats/sex/group) were exposed 6 hours/day for 10 weeks at 0, 400, 3000, or 8000 ppm of MTBE vapor, then mated within groups for 3 weeks to produce the F_1 generation. Exposures to the parental animals continued through day 19 of gestation and lactation (commencing on day 5). Selected F_1 weanlings (25/sex/group) were exposed at the same concentrations of MTBE for 8 weeks and then mated to produce the F_2 generation. During exposures at 3000 and 8000 ppm, F_0 and F_1 parental animals were hypoactive and exhibited no startle reflex; animals at 8000 ppm were ataxic. During premating, body weight gain and food consumption were reduced at 8000 ppm in F_0 males and in females of both generations (with significant reductions in the F_1 females compared to controls) and transiently were reduced in males and females in the 3000-ppm F_1 males and females. Lactational body weights were increased in the 8000-ppm females from both generations; increased liver weights were noted in the two high-dose groups for both F_1 males and females, without treatment-related effects on histopathologic examination. No treatment-related reproductive effects were noted. Offspring survival were equivalent in all groups (except for a significant increase of dead F_2 pups on postnatal day 4 in the 8000-ppm group); there were reportedly no remarkable post-mortem findings. In F_1 offspring, body weights were decreased at 3000 and 8000 ppm for days 14 to 21 and 21 to 28, respectively. During F_1 lactation, maternal food consumption was reduced at 8000 ppm; F_2 pup body weights were reduced among litters inhaling 3000 or 8000 ppm for postnatal days 14 to 28 and 7 to 28, respectively. No effect of maternal exposure was noted on postnatal death rates. The authors[83,84] stated that the NOEL for adults and offspring was 400 ppm, indicating no increased risk to the offspring in the absence of adult toxicity; the NOEL for reproductive toxicity was a least 8000 ppm.

Genotoxicity Studies

Two samples of MTBE tested in *Salmonella* or *Saccharomyces* in the presence or absence of metabolic activation were negative. MTBE was tested in a mouse lymphoma forward mutation assay both in the presence and absence of metabolic activation. When tested with S9 activation, the test material showed a dose-related mutagenic effect; the test material was toxic at 2.125 μL/ml with a dose-related mutagenic effect attributed to the production of formaldehyde as a reactive intermediate. When tested without activation, MTBE gave negative results; some toxicity was observed at concentrations greater than 6.25 μL/ml.[26,86]

In sister-chromatid exchange (SCE) and chromosomal aberration assays, MTBE produced negative results when tested at doses ranging from 0.004 to 5.0 μL/ml. However, an increase in SCE was observed at 0.2 and 1.0 μL/ml with activation in one sample.[11]

An *in vivo* evaluation using *Drosophila melanogaster* found that MTBE was nonmutagenic in the sex-linked recessive lethal test in wild-type Oregon-R males exposed to 0.03%, 0.15%, and 0.3% MTBE dissolved in aqueous sucrose.[86,87]

MTBE was tested in an *in vivo* cytogenetic study in rats and subacute dosing regimens of up to 0.4 ml/kg failed to indicate a clastogenic effect; no evidence of clastogenic effect was found.[11] In another study,[86,88] *in vivo* bone marrow cytogenetic assays were performed using male and female Fischer 344 rats exposed 6 hours/day for 5 consecutive days at 0, 800, 4000 and 8000 ppm MTBE vapor. The predominant type of chromosomal aberrations observed were chromatid breaks and fragments, with the frequency within the range of spontaneous frequency in these animals and with the concurrent controls. MTBE failed to produce statistically significant or exposure-related increases in the number of chromosomal aberrations in exposed male or female F-344 rats.[86,88]

MTBE has been shown to be mutagenic in the activated mouse lymphoma assay when tested in the presence, but not the absence, of a rat liver-derived metabolic activation system.[89] Mackerer et al.[89] used a modified assay in which the enzyme formaldehyde dehydrogenase and its co-factor NAD+ were added in large excess so that any formaldehyde produced in the system was rapidly converted to formic acid. With MTBE exposure, there was a dose–response increase in the

frequency of mutants and cytotoxicity without the enzyme, and this response was greatly decreased with the addition of the enzyme and its cofactor. The authors[89] stated that formaldehyde derived from MTBE was responsible for the mutagenicity of MTBE in the activated mouse lymphoma assay.

Casanova and Heck[90] examined the formation of DNA protein crosslinks and RNA formaldehyde adducts from MTBE exposure in freshly isolated hepatocytes of female CD-1 mice, in addition to hepatocytes from B6C3 F_1 mice and male F344 rats; the authors[90] stated that the lack of concentration dependence and the absence of species or sex differences in the formation of the DNA protein crosslinks and RNA formaldehyde adducts indicated that the metabolism of MTBE to formaldehyde was not a critical component of the carcinogenic mechanism of MTBE in mice.

McKee et al.[91] assessed *in vivo* genotoxicity using the *Drosophila* sex-linked recessive lethal test, the rat bone marrow cytogenetics test, the mouse bone marrow micronucleus test, and the *in vivo–in vitro* unscheduled DNA synthesis test in the mouse; all tests were negative. The authors[91] stated that this indicated that the potential for *in vivo* mutagenic activity of MTBE was low and that any tumorigenic activity of MTBE was probably the result of nongenotoxic processes.

Pharmacokinetic/Metabolism Studies

Animals

The major metabolites of the oxidative demethylation of MTBE *in vivo* are methanol and tert-butanol; formaldehyde and tert-butanol were the principal products of hepatic microsomal oxidation by the P-450 system.[92] MTBE and tert-butanol concentrations in the blood, brain, and adipose tissues after inhalation were dose-dependent; tert-butanol provided an estimate of the total amount of MTBE distributed to peripheral drug metabolizing compartments.

More than 99% of MTBE absorbed after inhalation in rats was exhaled intact by 4 hours; the half-life of MTBE in blood of rats was about 30 minutes.[11,14,93–99] MTBE was metabolized to TBA (half-life in rat blood about 1.5 to 3.5 hours) and methanol, and the latter was then metabolized to formic acid. In the instillation of MTBE into gallbladders of dogs, the amount of MTBE in the systemic circulation was not detectable (< 100 μg/cc in all blood samples).[47]

Bernauer et al.[100] evaluated the biotransformation of ^{13}C-labeled MTBE (and labeled ethyl tert-butyl ether) into urine metabolites after an inhalation exposure at 2000 ppm for 6 hours in Fischer F344 rats using nuclear magnetic resonance and gas chromatography/mass spectrometry. tert-Butanol was a minor product of the biotransformation of MTBE; in addition, small amounts of a tert-butanol conjugate (possibly glucuronide) and acetone were identified. 2-methyl-1,2-propanediol, 2-hydroxy-isobutyrate, and another tert-butanol conjugate (possibly a sulfate) were the major metabolites. Additional studies on tert-butanol suggested that it was intensively metabolized by further oxidation reactions.

In a series of studies,[93–97] male and female Fisher 344 rats were given single intravenous (40 mg/kg), dermal (40 and 200 mg/kg in occluded chambers), and oral doses (40 and 400 mg/kg) of ^{14}C-labeled MTBE and then some were nose-only exposed to MTBE vapor for single 6-hour intervals at concentrations of 400 or 8000 ppm or for repeated, daily, 6-hour, vapor exposures at 400 ppm for 15 days. The mean total recoveries of ^{14}C ranged from 70% to 80% of the dose after all routes of acute administration. The absorption of ^{14}C-MTBE was virtually complete after oral dosing and limited (14%–17% at the low dose and 35%–36% at the high dose) after dermal exposure. After intravenous, oral, and dermal routes, most of the absorbed ^{14}C was recovered in the expired air (42%–47% of the intravenous; 46%–55% of the low oral dose; 65%–69% of the high oral dose; 6%–10% of the low dermal dose; 23%–24% of the high dermal dose); most of the ^{14}C was present as MTBE, with a small proportion due to tert-butanol. For inhalation at single and repeated low-dose exposures, 65% to 71% of the ^{14}C was recovered in the urine, while at high-dose inhalation, 54% to 59% was recovered in exhaled air. In urine, most of the ^{14}C was present as 2-methyl-1,2-propanediol and α-hydroxyisobutyric acid (oxidation products of tert-butanol). Fecal recovery of ^{14}C was < 1%. At 48 hours postexposure, virtually all the ^{14}C was eliminated from the rats, regardless of route. Plasma concentrations of MTBE and tert-butanol, determined by gas chromatography, were lower in females when compared to males after intravenous and oral administration but not after inhalation exposure; ^{14}C recovery was lower in the urine but higher in the expired air of females. Regardless of the route of exposure and sex, the authors[93–97] described the pharmacokinetics of MTBE by a one-compartment open model. The $t_{1/2}$ of MTBE was 0.5 hour, regardless of route. There was a rapid first-pass clearance of MTBE from the lung after intravenous administration compared with the oral route; there was saturation of metabolizing enzymes at the higher doses suggested by higher recoveries in expired air at the high oral and inhalation doses. There was a shorter $t_{1/2}$ for tert-butanol after repeated inhalation when compared to a single inhaled exposure suggestive of enzyme induction.[93–97,101,102]

In 3-month-old male Wistar rats exposed 6 hours/day, 5 days/week for 2 to 15 weeks at 0, 50, 100 or 300 ppm of MTBE vapor, circulating

concentrations were dependent on the inhaled concentration of MTBE after 2 weeks of exposure; blood concentrations of tert-butanol were also dose-dependent.[59,60] After 6 weeks, the blood ether concentrations decreased at 50 ppm MTBE but remained unaffected at the higher dose levels; TBA concentrations increased after 6 weeks with all doses and then began to decrease. The brain concentration of MTBE was linearly correlated with its blood concentration; high ether concentrations in adipose tissue are also explained by its high lipophilicity.[59,60]

Poet and Borghoff[103] reported that the uptake of MTBE was 5.5 times greater in the male than the female F-344 rat kidney homogenate. Using ^{14}C-labeled MTBE, the uptake of MTBE in the male kidney (but not the female) was found to be dependent on protein and chemical concentrations. A two-compartment vial equilibration model was used to assess the interactions between MTBE and α_2-microglobulin proteins.

Metabolism of MTBE (in concentrations up to 5 mmol) by rat hepatic microsomes prepared from acetone- or phenobarbital-treated Sprague–Dawley rats resulted in equimolar amounts of tert-butanol and formaldehyde; demethylation increased significantly after acetone and phenobarbital pretreatment.[104] Monoclonal antibodies against the cytochrome P-450IIE1 isoenzyme resulted in 35% inhibition of MTBE metabolism, suggesting a partial role for this enzyme in MTBE metabolism. MTBE and its metabolite tert-butanol may be an inducer of its own metabolism.[104]

Borghoff et al.[105] have attempted to develop a physiologically based pharmacokinetic model of MTBE and tert-butanol in male Fischer 344 rats since both compounds cause renal tumors with chronic exposure in male rats. MTBE metabolism was described in the model as occurring in two saturable pathways and was able to predict gas uptake and blood levels of MTBE exposed by inhalation, intravenous, and oral administration. Tert-Butanol blood levels were predicted, based on a low MTBE exposure concentrations using a two-compartment model. The pharmacokinetics of tert-butanol appear to be more complex than MTBE, requiring additional experimental data.

Hong et al.[106] evaluated the metabolic activity of the olfactory mucosa of male Sprague–Dawley rats with exposure to MTBE, ETBE and tert-amyl methyl ether (TAME). The metabolic activity was reportedly 46-fold higher in the nasal mucosa than in the liver in the metabolism of MTBE; no detectable activity was found in the microsomes from the lungs, kidneys, and olfactory bulbs of the brain. As with the livers, the metabolic activity was dependent on NADPH and inhibited by carbon monoxide. Because tert-butanol and formaldehyde have been reported as metabolites of MTBE, the authors[106] speculated that the rapid nasal metabolism and irritating metabolites of MTBE may contribute to the multiple symptoms reported by some humans exposed to MTBE inhalation.

Humans

Hong et al.[107] evaluated the role of the cytochromes P-450 in the metabolism of MTBE in human livers. The human liver was shown to be active in the metabolism of MTBE to tert-butanol; the activity was localized in the microsomal fraction but not the cytosol. Formation of tert-butanol in human liver microsomes was NADPH-dependent and significantly inhibited by carbon monoxide; the authors stated[106] that this suggested that the cytochrome P-450 enzymes play a critical role in the metabolism of MTBE. Human cytochrome P-450-2A6 and 2E1 cDNAS were evaluated. The heterologously expressed 2A6 was more active in the metabolism of MTBE, as well as ETBE and TAME. Additional studies by Hong et al.,[108] using 2E1 knock out mice, demonstrated that 2E1 plays a negligible role in the metabolism of MTBE and the other fuel oxygenates in mouse livers. The authors[106] suggested that these results may explain the possible presence of human subpopulations with sensitivity to MTBE, based on individual genetic ability to metabolize MTBE.

The distribution and excretion of MTBE and its metabolites has been studied in humans during and after percutaneous transhepatic litholysis with MTBE.[22,109] Any MTBE that was not removed during this procedure escaped into the gut and absorbed into systemic circulation. Thus, MTBE was exhaled, distributed to fatty tissues, and excreted renally with its major metabolite, tert-butanol. In a study of MTBE used for cholelithiasis in 27 humans (mean treatment time 5.1 hours at doses ranging from 1 to 15 cc),[109] MTBE and its metabolites were determined in blood at concentrations of 0.04 mg/ml of MTBE during treatment, with only traces found 12 to 18 hours after cessation of treatment.[109] At treatment end, MTBE was found at 0.018 mg/ml urine, with the metabolite tert-butanol at 0.04 mg/ml. After 12 to 18 hours, the tert-butanol level had dropped to 0.025 mg/ml. Methanol was found as trace levels only in three patients; formic acid and formaldehyde were absent. MTBE concentration in fatty tissue was 0.135 mg/g (0.068–0.303 mg/g) in a mean treatment time of 9.5 hours. The authors[64] estimated that the body burden of MTBE at treatment end would be 2.85 g in a human male with a fat weight of 12.4 kg and 3.55 g in a human female with a fat weight of 22.26 kg. In one patient (4 weeks post-cesarean delivery) treated with MTBE for 4 hours, the MTBE and tert-butanol levels in breast milk during treatment were slightly less than those of blood; the tert-butanol breast milk concentration was higher than the blood concentration after 28 hours.[110]

Amberg et al.[110] evaluated the biotransformation and kinetics of MTBE excretion in healthy adult

humans (3 males and 3 females) and F344 NH rats (5 each) exposed at 4 and 40 ppm MTBE for 4 hours. MTBE blood levels were 5.9 ± 1.8 μmol in rats and 6.7± 1.6 μmol in humans at the 40-ppm dose, and 2.3 ± 1.0 μmol and 1.9 ± 0.4 μmol in humans at the 4-ppm level. MTBE was rapidly cleared with a half-life of 2.6 ± 0.9 hours in humans and 0.5 ± 0.2 hours in rats; tert-butanol was cleared with a half-life of 5.3 ± 2.1 hours in humans. Between 35% and 69% of the MTBE retained after the end of exposure was recovered as metabolites in the urine of both humans and rats; 2-methyl-1,2-propanediol, 2-hydroxyisobutyrate, and tert-butanol were all identified with elimination half lives of 7.8 to 17 hours in humans. The authors[110] concluded that the biotransformation and excretion of MTBE were rapid and similar between rats and humans.

In chamber studies, two healthy young human volunteers exposed for 1 hour at 5 mg/m^3 of "pure" MTBE, had blood levels that rose rapidly without plateau during exposure. Peak MTBE concentrations in the two subjects were 8.2 and 14.1 μg/L. After exposure, blood concentrations fell rapidly with half-lives of 36 and 37 minutes; by 7 hours postexposure, the concentrations had fallen to 0.2 and 0.6 μg/L. Blood tert-butanol concentrations rose steadily during exposure and maintained a steady concentration of 7 to 10 μg/L up to 7 hours postexposure. In other chamber studies, the half-life of inhaled MTBE in blood was estimated to be 60 minutes, while that of tert-butanol appeared to be several hours to a few days.[14,111]

In chamber studies, Johanson et al.[112] evaluated the toxicokinetics and reported acute symptoms of MTBE and other similar fuel additives in ten healthy male volunteers exposed at 5, 25, and 50 ppm for 2 hours of light exercise. Low uptake (32%–42%), high postexposure exhalation (20%–33%), and low blood clearance were reported consistent with relatively slow MTBE metabolism compared to other solvents. The kinetics of MTBE were similar to ETBE and TAME. There was less than 1% update of tert-butanol in the urine, consistent with further metabolism of tert-butanol. The half-life of tert-butanol was 7 to 10 hours in blood and urine, recommending it as a possible biomarker for MTBE exposure. The concentration of MTBE and TBA were proportional, indicating linear kinetics at least to 50 ppm exposure.

Cain et al.[113] evaluated the blood levels of MTBE in pharmacokinetic chamber studies on four healthy adult subjects with 1 hour of exposure at 1.7 ppm MTBE. The MTBE blood concentrations rose 20-fold from baseline to 17 ìg/L by the end of exposure and declined rapidly to one half that level within 40 minutes postexposure. Attempts to quantify tert-butanol in the blood had poor reproducibility, although there appeared to be a similar concentration magnitude with a slower rate of decline compared to MTBE.

White et al.[37] evaluated venous blood samples from 14 commuters and 30 other individuals working in the vicinity of automobiles or traffic in Connecticut. Samples were analyzed for MTBE, tert-butanol, benzene, m/p-xylene, o-xylene, and toluene. Blood levels of tert-butanol correlated highly with breathing zone samples of MTBE and with blood levels of the other volatile organics. The estimated correlation coefficient was 0.80 between air MTBE and blood MTBE ($p = 0.0001$) and 0.70 between air MTBE and blood tert-butanol ($p = 0.0001$).

Vainiotalo et al.[30] and Saarinen et al.[114] evaluated exposure to MTBE and TAME from gasoline during tank loading in Finland. The geometric mean of MTBE was 4.3 to 6.4 mg/m^3 (somewhat higher in the summer) with an overall range of 0.75 to 33.7 mg/m^3; there was a statistically significant linear correlation between MTBE in the breathing zone with blood ($r = 0.86$, $p = 0.0001$) and with urine, but there was no correlation between MTBE in air and tert-butanol in blood or urine.

Human Studies

A number of reviews exists covering the relatively sparse data concerning the known and potential human health effects of MTBE exposure.[9,10,27,41,42,115]

Medicinal Use

The majority of the human studies, including case history reports and case series, relate to transhepatic instillation of MTBE into the gallbladder to dissolve cholesterol radiolucent gallstones. There was a plethora of reports in the medical literature concerning this intervention over the last few years.[12,23,109,116–127] In this technique, MTBE was continuously infused and withdrawn from the gallbladder (usually via percutaneous transhepatic catheter) in amounts to fill the gallbladder (1 to 15 cc) for up to 6 hours/day for 1 to 3 days.

Side effects were reported in 10% to 100% of treated patients. Patients complained of nausea, vertigo, vomiting, and abdominal discomfort, all of which could be controlled by reducing the infusion rate and keeping the amount infused as low as possible or by discontinuing treatment. In rare cases, transient hypertension and angina occurred which ceased with cessation of therapy.[117–121] Mild, transient increases in liver transaminase enzymes, which returned to normal within a few days, have been reported.[123] Patients who developed cholangitis or local peritonitis as evidenced by leukocytosis, fever, and abdominal pain after the intervention responded to parenteral antibiotic treatment.[119,121,128]

Overflow of MTBE during instillation was associated with sedation, the unpleasant odor of MTBE on the breath, and a burning upper abdominal and back pain. One patient was reported with severe complications secondary to overflow, including sedation resulting in reversible coma and MTBE

odor on the breath, followed by acute renal failure with anuria which finally resolved with dialysis.[124] It is not clear if the renal failure was due to the MTBE or the possible metabolism of methanol to formic acid (the latter is a known cause of renal failure).[59] After MTBE instillation 1 year previous, two patients were shown to have an abnormal dilation of the common bile duct via cholangiography.[23] As a result of local chemical toxicity, mild duodenitis has been reported in other cases associated with MTBE overflow from the gallbladder into the duodenum. The duodenitis was rapidly reversible (as seen in rabbits); a single oral dose of activated charcoal can be used preventatively to absorb the MTBE if there was spillage into the gut.[55,117,122,125,127] As with dogs, damage to the gallbladder mucosa in humans was not attributed to MTBE, but rather to the stones themselves.[109] Deaths associated with this treatment have been attributed to the stones and mechanical intervention (i.e., cholangitis) rather than to MTBE itself.[120]

There have been complaints from workers, as well as patients, exposed to the MTBE administered for gallstone therapy in radiology suites. Despite closed systems, the unpleasant odor seeps into the ambient air, causing headache, nausea, nasal congestion, and eye irritation in personnel and other visitors; no specific air levels were reported. Recommendations have been made to administer the MTBE instillation only in well-ventilated suites separated from high traffic areas and with scrupulous attention to any potential sources of sparks from electrical equipment or from designated smoking areas.[116,117,125,127]

MTBE as a Gasoline Additive

CHAMBER STUDIES

Cain et al.[113] evaluated 43 subjects exposed in a double-blind study to a mixture of 1.7 ppm MTBE and 7.1 ppm volatile organic compounds (VOCs) and air. Subjects rated their symptoms, mood, environmental parameters, and took computerized neurobehavioral performance tests; measures of eye irritation (tear film break up, redness) and nasal inflammation (polynuclear neutrophilic lymphocytes) were made pre- and postexposure. There were no exposure-related differences except for an increase in the number of nasal inflammation (polynuclear neutrophilic lymphocytes) after VOC exposure, especially at 24 hours postexposure.

In chamber studies, Johanson et al.[112] evaluated the toxicokinetics and reported acute symptoms of MTBE and other similar fuel additives in ten healthy male volunteers at 5, 25, and 50 ppm for 2 hours of light exercise. The subjective rating of solvent smell increased dramatically as the volunteers entered the chamber and declined slowly with time during exposure; the rating of solvent smell increased with increasing solvent exposure. Blocking index (an index of nasal swelling) increased significantly over time ($p=0.03$) but without a dose–response relationship and without confirmation using acoustic rhinometry. No other effects were reported, and no dose–response for subjective ratings of discomfort was established, including objective eye (redness, tear film break up time, conjunctival damage, and blinking frequency) and nasal (peak expiratory flow, acoustic rhinometry, and inflammatory markers in nasal lavage) effects.

As a result of complaints associated with the use of MTBE in gasoline, controlled human chamber studies with MTBE were performed.[14,111] Thirty-seven healthy, nonsmoking individuals (19 females) between the ages of 18 and 35 were exposed for 1 hour to both clean air and 1.39 ppm (5 mg/m^3) "pure" MTBE on different days in chambers with controlled temperature (75°F) and humidity (40%). Pre/post-symptom questionnaires, cognitive testing (NES II Battery), and objective measures of ocular (tear film and ocular hyperemia) and nasal (odor threshold and nasal lavage for cytology and inflammatory cells) irritation were made. The only significant difference was that female subjects rated the clean air as better air quality than the MTBE air. Seventy-six percent of the participants correctly identified the odor of MTBE at 0.24 μL/L. No MTBE-induced headaches or nasal irritation were reported, based on questionnaire, nor did MTBE affect the battery of neurobehavioral tests. MTBE exposure did not induce eye irritation or inflammation. There was reportedly sufficient statistical power to detect changes for irritation and headache in this study; other chamber studies have upheld these conclusions.

ORAL EXPOSURE

Headache, dizziness, nausea, and dyspnea were reported in a family of five who were exposed through baths, laundry, and dishwashing, but not through drinking, to water contaminated with gasoline containing MTBE as an additive. The levels of MTBE reported from the well-water analysis were 1260 to 1610 μg/L. In a double-blind odor test, all members of this family indicated MTBE as the most objectionable odor.[18]

Vojdani et al.[129] evaluated a group of 60 subjects (38 men and 22 women) exposed to MTBE- (concentrations 1– 76 ppb) and benzene- (0.214 ppb) contaminated water for periods of 5 to 8 years compared with a group of 32 healthy subjects (17 men and 15 women) with a similar age distribution without any exposure history. None of the controls or cases had any chronic disease by medical history, and persons with occupational exposure to solvents were excluded. The exposed group reported many symptoms (including anxiety [50%], difficulty concentrating [56.6%], and severe headache [81.6%]) but the control group allegedly reported none of these symptoms. Apoptotic lymphocytes were compared between the groups, reportedly with statistically significant differences between the mean

for each group (26.4 ± 1.8 versus 12.1 ± 1.3 respectively; $p < 0.0001$). The authors[129] stated that this indicated an increased rate of apoptosis in 80.5% of exposed individuals. In addition to a lack of exposure data, it was not stated if these data were collected from subjects blinded to the hypotheses or analyzed by blinded investigators.

Respiratory exposure

After the introduction of MTBE-containing gasoline during the winter of 1992 to 1993 in several northern states (Alaska, Montana, Colorado, and New Jersey) to decrease carbon monoxide production from internal combustion engines during these cold months, the U.S. EPA received complaints of nausea, headaches, and dizziness in workers and commuters exposed to exhaust or gasoline fumes containing MTBE. A 95% reduction in carbon monoxide levels was recorded in these same areas, which was attributed to the addition of MTBE to gasoline.[15]

A complaint survey of consumers and workers was completed by the API, as well as other surveys by the CDC and the state of Alaska. The complaints recorded were most numerous in Alaska during October and November at the start of the winter season. Mehlman[130] reported that a hotline was established in New Jersey for residents calling with MTBE symptom complaints shortly after its introduction in the Winter 1992. Over 800 people reportedly called; a symptom questionnaire was sent to 265 of these individuals. Of these, 235 individuals, all were New Jersey consumers operating vehicles using fuels that contain MTBE, who responded with allegedly neurotoxic, respiratory, and allergic symptoms (including headache [74.5%], light-headedness [53.6%], sinus problems [68.1%], ear/nose/throat complaints [68.9%], and breathing problems [49.4%]). Mehlman also briefly mentioned a high frequency of complaints among workers in oil refineries exposed to MTBE. Another report by Mehlman[131] described the cases of several patients with a detailed history of symptoms alleged to correlate with exposure to MTBE. No control groups were used, nor were any exposure data presented.

Gordian et al.[132] performed an ecological study in which they analyzed outpatient visits for state employees and dependents (n = 28,000) living in Alaska over three winters using health insurance claims to assess the possible effects before and after the introduction of MTBE as a fuel additive. In particular, odds ratios for visits for upper respiratory illness, bronchitis, headache, and asthma were examined. There was no significant increased risk of visits for these illnesses after the introduction of MTBE.

Mohr et al.[133] performed a cross-sectional study of self-reported symptoms among 237 garbage workers in New Jersey with high (115) and low (122) MTBE environmental exposures. Data were collected on symptom frequency over the past 30 days and pre/postshift symptoms. No differences were found. Both groups had increased reported symptoms at the end of their shifts, but there was no difference between the two groups. A subpopulation of those workers (known as fuelers) who fueled their trucks more than 5 hours/day had no differences over the same previous 30 days; the higher exposure group of the fuelers did have increased report of symptoms after their shift, but when compared with age, sex and education-matched controls, this difference was eliminated. The authors[13] concluded that no reported symptoms could be attributed to the MTBE exposure in this particular occupational cohort.

Fiedler et al.[134] assessed 14 individuals with reported sensitivities to very low level chemical exposure (i.e., multiple chemical sensitivity), 5 chronically ill persons with the diagnosis of chronic fatigue syndrome, and 6 normal control subjects of comparable age, education, gender, and ethnicity to evaluate response to situations where there was possible exposure and lack of exposure to gasoline with MTBE. Using a telephone-structured interview, the Wahler Physical Symptoms Inventory (physical symptoms over the past year), and the Symptom Amplification Scale (indication of hypervigilance to bodily sensations), both disease groups reported significantly more symptoms during the past year than normal controls; they also reported increased frequency of symptoms associated with MTBE (such as headache, burning in the nose and throat, etc.) in all situations, regardless of possible MTBE exposure. The multiple chemical sensitivity subjects did not report significantly higher symptoms not associated with MTBE (e.g., chills, diarrhea, etc.). The authors[134] concluded that MTBE symptoms were not uniquely associated with chemical sensitivity or with situations where MTBE exposure would be more prevalent.

Hakkola et al.[135] evaluated the occurrence of neuropsychological symptoms over 1 week and over 1 month among 101 gasoline tanker drivers from 3 Finnish oil companies using gasoline with 10% MTBE; controls were 100 milk delivery workers. Work history, gasoline and ethanol exposure, and health status were evaluated and as standardized symptom interviews were utilized. There were no significant differences in reported neuropsychological symptoms among the tanker drivers and controls. A nonsignificant association was seen in reported sensory and motor symptoms among the tanker drivers compared to controls. Increased age, reported chronic disease, and poor perceived health status were associated with increased reported symptoms. Additional study by Hakkola et al.[136] on the same study population was performed to evaluate pre/postwork week effects of MTBE/gasoline exposure using a neuropsychological screening questionnaire (including modified POMS). The occupational hygiene measurements among Finnish tanker drivers were C_5 to C_{11} hydrocarbons (during

bottom loading 32–589 mg/m^3; 75–628 mg/m^3 during delivery) and MTBE (3–42 mg/m^3; 4–98 mg/m^3). The tanker drivers scored significantly higher on the fatigue scale pre/postwork week; in particular, tanker drivers with higher gasoline exposures scored higher fatigue scores than those with shorter gasoline exposures. During exposure, 20% of the tanker drivers versus 1% of the controls reported acute symptoms which consisted of headache, dizziness, nausea, dyspnea, or irritation of saliva excretion.

Moolenar et al.[38] of the CDC and the Alaska Health Dept evaluated 18 workers (service station attendants, garage workers, drivers, and mechanics) during the active use of MTBE as a gasoline additive in December 1992 and 28 workers after the use of MTBE was suspended in February 1993. All workers were heavily exposed to motor vehicle exhaust or gasoline fumes, with a significant decrease in MTBE blood levels from December until February as reported above. Workers in February reported almost no symptoms associated with MTBE while the majority of workers in December reported these symptoms (e.g. headache 72% versus 4%); eye irritation 67% versus 7%; burning sensation 50% versus 0; dizziness 44% versus 0). There was a nonstatistically significant relationship between the highest quartile of blood MTBE concentrations and key health complaints associated with MTBE, not with other health complaints in December.

White et al.[37] evaluated venous blood samples from 14 commuters and 30 other persons working in the vicinity of automobiles or traffic in Connecticut. Samples were analyzed for MTBE, tert-butanol, benzene, m/p- xylene, o-xylene, and toluene. The highest levels of MTBE were found among gasoline service station attendants and the lowest among commuters. The odds ratio for reporting one or more key symptoms associated with MTBE exposure (e.g., headache, irritated eyes, burning of the nose and throat, etc.) predicted by the level of MTBE in the blood was statistically significantly elevated at 8.9 (95% confidence interval [CI] = 1.2–75.6). The commuters were interviewed about their symptoms in the morning and the other persons were interviewed at the end of the day, leading to concerns about comparability of responses. Nevertheless, the subgroup of noncommuters showed a highly significant association between reporting of MTBE symptoms and MTBE blood level (odds ratio = 21.0; 95%CI = 1.8–539.0). None of the workers reported symptoms not associated with MTBE (e.g., diarrhea, difficulty breathing, skin irritation, fever, etc.); there was a low prevalence of cigarette smoking and no correlation with symptoms and carboxyhemoglobin levels.

Vojdani et al.[137] evaluated two groups of subjects: 24 subjects (6 females and 18 males from 21–58 years) employed at least 2 years in gasoline service stations with gasoline emission exposure, and 12 healthy controls (4 females and 8 males 24–60 years) with no history of gasoline exposure beyond refueling once/week. An MTBE antibody assay (IgG and IgM) was developed and used. The exposed subjects were statistically significantly more likely to have higher levels of IgG and IgM MTBE than controls ($p<0.001$). The exposed subjects were more likely to report one or more symptoms associated with MTBE exposure (e.g., headache, fatigue, burning eyes and nose, etc.); however, there were no correlations between the number and severity of the reported symptoms with the antibody levels.

TLV Recommendation

Based on extrapolation from respiratory irritation in mice with MTBE inhalation exposure, Tepper et al.[48] estimated that 500 mg/m^3 (139 ppm) would be considered an 8-hour exposure limit for healthy humans to guard against significant sensory irritation. Tritapepe et al.[47] stated that the NOAEL for rats was 800 ppm for subchronic MTBE exposure; this was confirmed in a similar study by Duffy et al.[50] In a reproductive/developmental study in rats, an increased incidence of dilated renal pelvis in the low- (300 ppm) and high-dose (3400 ppm) females was noted.[77] After exposure during pregnancy to MTBE vapor,[78] the NOEL for maternal toxicity was 1000 ppm, and the NOEL for developmental toxicity was 8000 ppm for New Zealand white rabbits. For CD-1 mice, the NOEL for both maternal toxicity and developmental toxicity was 1000 ppm.[78–82] In a two-generation MTBE inhalation study in rats,[83,84] the NOEL for adults and offspring was 400 ppm with no increased risk to the offspring in the absence of adult toxicity; however, there was no dose–response relationship in this study.

In an internal report to the U.S. EPA, Clegg[138] developed a preliminary assessment of the developmental toxicity of MTBE based on the lowest-observed-adverse-effect level and NOAEL of Neeper–Bradley et al.[83,84] described above. Using uncertainty factors of 3 for extrapolation from rats to humans and of 10 for sensitive human populations, Clegg gave a preliminary estimate of 13.3 ppm (48 mg/m^3) to which no adverse developmental toxicity was likely to occur in humans, including a sensitive population. The U.S. EPA[14] warned that this must be considered preliminary and an estimate because no information exists in animals or humans to determine this more accurately.

Therefore, with Johanson et al.[112] noting no symptoms noted in a chamber study of ten human subjects up to 50 ppm, a NOAEL for repeated inhalation exposure of rats at 800 ppm,[51] the NOAEL of 400 ppm in rats from a two-generation study,[83,84] with renal toxicity noted in rats (both the dams and offspring) after inhalation of 300 and 3400 ppm,[77] and taking into account the preferred value approach, a TLV–TWA of 50 ppm is recommended.

At present, most occupational exposure to MTBE is through exposure to gasoline; in this case, the TLV for gasoline should be consulted. Also of

note is the use of MTBE in transhepatic instillation for treatment of gallstones; at this point, there exist no relevant data for exposed healthcare workers.

Given the above data of predominantly negative mutagenicity[53,54,71] and the significantly increased cancers in both sexes of mice and rats, particularly the α_2-microglobulin male rat kidney tumors and female mouse hepatic tumors,[9,10,17,27,39–41,43] MTBE is classified as an A3, Confirmed Animal Carcinogen with unknown relevance to Humans. Zhang et al.[139] used the Computer Automated Structure Evaluation (CASE) and the Multiple Computer Automated Structure Evaluation (MULTICASE) programs to correlate chemical structure with toxicologic activity for MTBE and several other fuel additives. Although the authors[139] noted that the experimental data regarding the effects in both humans and animals were lacking, MTBE was not predicted to be a human carcinogen. The authors also noted that MTBE was carcinogenic only at toxic exposure levels. At present, there is insufficient evidence to evaluate the carcinogenicity of MTBE to humans.

Although crucial to the long-term use of MTBE as an important fuel additive, the issues of environmental and drinking water contamination with MTBE and the possible carcinogenic and other health risks to humans are beyond the scope of this Documentation since this does not represent a typical occupational exposure scenario.[19–21] Also beyond the scope of this Documentation is a discussion of the potential human health and environmental benefits secondary to air pollution reduction through the use of MTBE as a fuel additive.[140–142]

No Skin notation is warranted given the available data (e.g., LD_{50} for a single cutaneous dose in rabbits was > 10 ml/kg)[3,6,25,45] nor were sufficient data available to assign a sensitization (SEN) notation or recommend a TLV–STEL. The reader is expected to be familiar with the section on *Excursion Limits* in the "Introduction to the Chemical Substance TLVs" of the current edition of the *Documentation of the TLVs and BEIs* for the guidance and control of excursions above the TLV–TWA, even when the 8-hour TWA is within the recommended limit.

TLV Chronology

1993: *Proposed:* TLV–TWA. 40 ppm
1994: TLV–TWA. 40 ppm
1994: *Proposed:* A3, Confirmed Animal Carcinogen with Unknown Relevance to Humans
1995: TLV–TWA, 40 ppm; A3
2000: *Proposed*: TLV–TWA, 50 ppm; A3
2002: TLV–TWA, 50 ppm; A3

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